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EDITORIAL COMMENT

Novel Potential Blood Biomarkers for Detection of Anthracycline-Related Cardiomyopathy in Childhood Cancer Survivors

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Long-term childhood cancer survivors treated with anthracyclines are at risk of developing heart failure up to decades after anthracycline exposure.[1,2] Current guidelines recommend life-long echocardiographic surveillance in childhood cancer survivors treated with a cumulative anthracycline dose ≥100 mg/m^2 and/or a chest-directed radiotherapy dose ≥15 Gy with the goal to detect and treat asymptomatic left ventricular dysfunction in an early phase to prevent progression to heart failure.[3] Blood biomarkers may serve as a cost-effective and accessible surveillance tool to reduce the need for echocardiography evaluations, or they may be used in combination with echocardiography to improve its diagnostic accuracy for detecting asymptomatic cardiac dysfunction. Previous studies mainly focused on natriuretic peptides and cardiac troponins and found a limited diagnostic value for detecting left ventricular dysfunction when used as individual biomarkers.[4-6]

In the present study published in this issue of *JACC: CardioOncology*, Poudel et al[7] sought to discover novel plasma biomarkers for anthracycline-related cardiomyopathy in long-term childhood cancer survivors exposed to anthracyclines without chest-directed radiotherapy.[7] The discovery cohort included 75 asymptomatic anthracycline-cardiomyopathy cases (ejection fraction 40%-49% or a 10% absolute drop from baseline) and 75 matched controls (ejection fraction >50%) from the St. Jude Lifetime cohort. Internal validation was performed in 23 cases with symptomatic cardiomyopathy (ejection fraction 20%-29%, or a 20% absolute drop from baseline, or requiring heart failure medication) and 23 matched controls also from the St. Jude Lifetime cohort. In the discovery cohort, 28 of the 867 proteins measured with mass spectrometry were differentially expressed at a false discovery rate of 25%, whereas none of the 218 metabolites were differentially expressed. Subsequently, multiple Lasso conditional logistic regression models were built including the top differentially expressed proteins. A combination of 27 proteins selected with the Lasso model performed best and had an accuracy of 98.7% in the discovery cohort and an accuracy of 82.6% in the validation cohort. The 27 identified proteins are known to be involved in various processes including inflammation and antigen recognition, cellular adhesion, cardiac hypertrophy, fibrosis, and mitochondrial function.

Strengths of the study include its matched design, the use of an untargeted mass spectrometry approach that allows for the identification of previously unknown proteins and metabolites in anthracycline cardiomyopathy, and the combined evaluation of biomarkers for their diagnostic performance using a multivariable model. The major limitation of the study is its small sample size and the lack of an external validation cohort, which potentially limits the generalizability of the results. In addition, due to the small sample size, the study could not evaluate the added predictive value of the identified proteins

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next to clinical risk factors for anthracycline cardiomyopathy such as cumulative anthracycline dose, sex, and the presence of hypertension, diabetes, obesity, and/or hypercholesterolemia.

Few previous studies focused on identifying novel blood biomarkers for anthracycline cardiomyopathy in childhood cancer survivors.[8-10] These previous studies had small sample sizes, and no external validation was performed. Interestingly, none of the previously identified blood biomarkers were replicated in the present study, possibly due to differences in study design, participant characteristics, definitions of left ventricular dysfunction, and/or biomarker analytical techniques. This lack of replication underscores the need for the evaluation of newly identified biomarkers in larger, independent external validation cohorts.

When exploring the underlying pathophysiological pathways of the identified biomarkers, there is potential overlap with previous studies. Seven of the 28 identified proteins are associated with immune system processes, specifically antigen recognition and chemoattraction, which is consistent with a previous study that identified specific chemokines as potential plasma biomarkers for anthracycline cardiomyopathy in childhood cancer survivors.[10] Additionally, studies in adult cancer survivors have identified inflammatory markers as biomarkers for anthracycline cardiomyopathy.[11,12] Mechanistic studies of anthracycline cardiomyopathy also suggest a role for the immune system in anthracycline cardiotoxicity, specifically the recognition of cell death-associated material by Toll-like receptors, which promote inflammation.[13] Thus, immune system markers may especially be an interesting target for future external validation efforts.

To conclude, Poudel et al[7] should be commended for this important and well-designed study on potential novel blood biomarkers in anthracycline cardiomyopathy. The identified protein biomarkers, if externally validated and clinically available, may help to reduce the need for life-long surveillance echocardiograms in the growing population of long-term childhood cancer survivors. Additionally, future studies may assess the predictive value of these biomarkers for the development of cardiomyopathy, which could aid in the risk stratification of survivors, inform the frequency of cardiomyopathy surveillance, and enable preventive interventions to delay or halt progression to heart failure.

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